ARIAD 3462-US

In The United States Patent And Trademark Office

Serial No. : 09/407,402
Filing Date : 9/28/99
Inventors : Natesan & Gilman
For : Chimeric Transcription Factors

Art Group: 1632
Examiner: Shukla, Ram R.

#13

Commissioner of Patents & Trademarks
Washington, DC 20231

March 11, 2003

Request for Three Month Extension & Response to Office Action

This is in Response to the Office Action mailed on 9/11/02, a response to which was originally due on 12/11/02. Applicants hereby request a three-month extension for responding and authorize the Commissioner to charge the fee for such extension to Deposit Account No. 01-2315. The new deadline is now 3/11/03, and this response should be considered timely filed.

1. Response to Restriction Requirement

Applicants again thank the Examiner for reconsideration of the restriction requirement. However, the restriction requirement remains confusing. Group II was elected based on the Examiner's prior indication that claims 1 – 38 would be examined together with whichever of Groups II – V were elected, because claims 1 – 38 recite embodiments common to the inventions of the other groups. See point 3, page 2 of the 1/23/02 Office Action. However, despite the fact that elected claim 40 of Group II depends on claim 6, according to point 3 on page 3 of the 9/11/02 Office Action, only claims 1 – 5 and 31 will now be examined with the Group II claims. We respectfully request reconsideration of point 3 on page 3 of the pending Office Action and hope that all of claims 1 – 38 will be examined together with the Group II claims 39 – 51 as previously indicated by the Examiner. Again, note point 3 on page 2 of the prior, 1/23/02 Office Action.

Assuming that was what was intended, and noting that the restriction to Group II has been made final, Applicants withdraw claims 52 – 67, but do so again under the traverse of record. To preserve the record in this case applicants note a number of factual matters which may have been misunderstood by the Examiner and which have led to what we consider to be erroneous aspects of the restriction rquirement:

(1) Applicants' prior traversal of the restriction was not simply on the ground that the grouping of claims 54 and 55 was incorrect. The traversal presented in the May 22, 2002 response had a number of bases, one of which was as follows: the description of Group III needs to be corrected, claims 54 and 55 need to be moved into group V or claims 56-59 need to be moved into Group III.

(2) The Examiner states that the invention of Group II is a cell and the invention of Group V is an organism. That is incorrect.

The invention of Group II is not (just) a cell. It includes (a) a method for engineering cells by introducing certain nucleic acids (claims 39 – 44) and (b) cells containing certain nucleic acids (claims 46 – 51).

The invention of Group V is not (just) an organism. It includes (a) a method for genetically engineering an organism by introducing certain nucleic acids (claim 56 – 59), and (b) stimulating target gene expression in those organisms by administering a ligand (claims 64 – 67).

The significance of that is as follows. Claim 44 of Group II, in which the cells are genetically engineered within an organism, logically overlaps the subject matter of Group V in which an organism is genetically engineered. As stated in applicants' prior response, because the two groups contain logically overlapping subject matter, their descriptions should be redefined or they examined together. Doing otherwise is an improper exercise of the authority to restrict prosecution in furtherance of efficiency.

(3) Applicants' point about the relationship between the nucleic acids of Group I and the genetic engineering methods, cells and organisms of the subsequent claims was not that the various nucleic acids are or are not patentably distinct from one another. Applicants' point was that those various nucleic acids of Group I are the same nucleic acids referenced in claims dependent on the Group I claims. Thus, a search of those dependent claims would seem to require at least the search required for the Group I claims. Because of that, examination of Group I with Group II, for instance, would not add a substantial burden on the PTO. This was laid out in applicants' prior responses.

(4) In contrast to the Examiner's statements, individual elements of a claim are themselves not necessarily embodiments or species of the invention. Each claim has to be read in its entirety in order to reflect the claimed invention and its various species. While a search of one element of a claim may not be coextensive with a search for another element of a claim, when a claim has two or more elements, the search must encompass all required elements—not just one or the other. Therefore, an applicant should not be forced to specify only one of two or more required elements of a claimed species. That is different from requiring an applicant to elect a true species of the invention containing a specified element from a group of possible choices for that element.

(5) To the extent that the Examiner sticks with the prior commitment to examine claims 1 – 38 with whichever other group is elected (point 3, page 2 of the 1/23/02 OfficeAction), applicants respectfully request reconsideration and withdrawal of the objection to claims 39 – 51 as dependent on withdrawn claims.

2. *Compliance with Sequence Listing Requirements*

Applicants have amended the specification to insert therein Seq ID numbers (from the sequence listing already of record in this case). The amended pages are included as an attachment hereto. Those amendments do not introduce any new matter and should bring the specification into compliance. Entry of these amendments is requested.

3. *Enablement under 35 USC §112*

Applicants appreciate the Examiner's acknowledgement that the claimed invention is enabled for practice with cells ex vivo, in embodiments based on various ligand binding domains (although the several domains noted by the Examiner included, unintentionally we assume, a number of transcription activation domains, rather than ligand binding domains).

However, the Examiner took the position that the specification is not enabling for practice of the invention in cases where the cells are present in vivo within an animal on the basis that (1) doing so was and remains unpredictable, as was (and is) the therapeutic use of gene therapy and (2) that animal experiments are not predictive of therapy for any disease. The Examiner also states that there are many variables involved in gene expression in vivo and that the specification doesn't provide guidance for dealing with such variables. The Examiner further relies upon a variety of other grounds for doubting that the invention can be practiced in vivo.

Applicants traverse these grounds for rejection.

First, while genetic engineering of whole animals, e.g.., introduction of genes in vivo, involves a number of variables and is a marvelous piece of science, it's practice is reliably carried out by those of ordinary skill in this art. Guidance for doing so is provided in the specification, e.g., on pages 35 - 40 and 58 - 60 and references cited therein (covering the introduction into animals of engineered cells or of nucleic acid constructs). It should be noted that the art was already well aware of materials and methods for introducing genes into animals for constitutive or regulated expression, including the use of a variety of viral vectors (adenoviral, AAV, etc.). See e.g. WO 94/18317, WO 96/20951, WO 96/06097, WO 97/31898 and WO 96/41865 for dimerization-based transcription regulation systems which have been used in the art for the successful engineering of whole animals.. For allostery-based counterpart systems which also have been used in the art for successcul engineering of whole animals see, e.g., US 5,654,168 and 5,650,298 (tet systems), and WO 93/23431 and WO 98/18925 (RU486-based systems)] or WO 96/37609 and WO 97/38117 (ecdysone/RXR-based systems).

As for gene delivery, the art was already aware of a variety of materials and methods, including viral and non-viral systems. For non-viral approaches, the art included among others, Felgner, et al., Ann NY Acad Sci 126-139, 1995; Canonico et al, Am J Respir Cell Mol Biol 10:24-29, 1994 (in vivo transfer of an aerosolized recombinant human alpha1 antitrypsin gene complexed to cationic liposomes to the lungs of rabbits); Tsan et al, Am J Physiol 268 (Lung Cell Mol Physiol 12): L1052-L1056, 1995 (transfer of genes to rat lungs via tracheal delivery of plasmid DNA alone or complexed with cationic liposomes); Alton et al., Nat Genet. 5:135-142, 1993 (gene transfer to mouse airways by nebulized delivery of cDNA-liposome complexes). The art was also aware of viral systems include those based on viruses such as adenovirus, adeno associated virus, hybrid adeno-AAV, lentivirus and retroviruses, which allow for transduction by infection, and in some cases, integration of the virus or transgene into the host genome. See, for example, Dubensky et al. (1984) Proc. Natl. Acad. Sci. USA 81, 7529-7533; Kaneda et al., (1989) Science 243,375-378; Hiebert et al. (1989) Proc. Natl. Acad. Sci. USA 86, 3594-3598; Hatzoglu et al. (1990) J. Biol. Chem. 265, 17285-17293 and Ferry, et al. (1991) Proc. Natl. Acad. Sci. USA 88, 8377-8381. See also. WO 96/41865, PCT/US97/22454 and USSN 60/084819, for example, for additional guidance on formulation and delivery of recombinant nucleic acids to cells and to organisms.

The foregoing is by no means a comprehensive list. The point is that the art was already well aware of materials and methods for delivery of genes to animals. The literature is and was replete with

examples of genetic engineering of whole organisms, and that knowledge base was and is available to the reader of applicants' specification. The specification need not and should not disclose again a detailed compendium of what was already known in the art.

As for the level of expression achievable, no particular expression level is required by the pending claims, and in fact, different expression levels may be desired in different embodiments. Applicants note that the Examiner's focus on therapeutic methods appears inappropriate. The Examiner is importing a limitation of achieving a therapeutic benefit into the claims, and is then rejecting the claims on the ground that the imported limitation is not enabled. The present claims encompass, but are not limited to therapeutic applications of the inventive method. As just noted above, therapeutic methods generally are enabled by the present specification. However, even if some particular therapeutic method were not specifically enabled, it is well established that even in an unpredictable art a patent applicant is not required to enable every species that falls within the scope of his claims. *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

Overall, the quantity of experimentation required in light of the content of the specification and the nature of the invention would be reasonably low. The specification does provide a wealth of practical information on design choices and implementation of the invention, some of which was noted by the examiner in the office action. A skilled practitioner reading the specification in light of the knowledge in the art would in fact readily be able to carry out the invention.

For these reasons, applicants respectfully request that this ground for rejection be reconsidered and withdrawn.

4. Novelty under 35 USC §102 and Priority Claim

As specified in the first paragraph of their specification, Applicants have a legitimate priority claim which in fact renders moot much or all of the grounds for rejection over the cited art. For instance, the '732 application specifically discloses the use of a p65 transcription activation domain in conjunction with a GAL4 DNA binding domain and a progesterone receptor domain or another hormone receptor such as described in WO93/23431 (see e.g., page 3, line 11 and page 4, lines 33 – 36 of the '732 application, copy attached). Notably, WO93/23431, incorporated by reference in the '732 application, clearly includes the use of an androgen receptor (see e.g. page 5, line 13 thereof). That disclosure in applicants' '732 application antedates the Burcin et al and Sui et al references. Reconsideration and withdrawal of the rejection based thereon is respectfully requested.

With respect to the rejection over Schmitz et al, the Examiner's position is that PMA is a ligand for TA1 or TA2, and that Schmitz et al thus disclose constructs encoding fusion proteins containing a GAL4 DNA binding domain together with a transcription activation domain and a ligand binding domain. Applicants respectfully disagree. As discussed in the last four paragaraphs of the Schmitz et al reference, beginning on page 15583, at best the authors suggest that PMA influences transcription not because it is a ligand for the fusion protein, but because PMA activates a kinase which phosphorylates TA2 directly or indirectly. Thus, there is no disclosure of a ligand binding domain to which PMA binds. Accordingly, reconsideration and withdrawal of this ground for rejection is respectfully requested too.

(DFDLDMLG) [Seq. ID No. 1], the related "V9" motif (DFDLDMLGG) [Seq. ID No. 2], a human activation motif such as the 14 amino acid acidic motif of human heat shock factor (HSF) or an alanine/proline-rich motif selected from p53 or CTF (preferably human) including such motifs which are homologous to alanine/proline rich motifs within residues 361 - 450 of p65. Alternatively, an activation domain such as amino acids 431-529 of HSF may be fused to p65 to form a composite activation domain. An exemplary composite activation domain (referred to as S3H) comprises the peptide sequence p65(281-551) linked to the peptide sequence HSF(406-530).

Transcription factors of this invention may be operatively linked to any promoter selected by the practitioner, including strong promoters such as CMV or weaker promoters like RSV, the MCK enhancer, or promoters for endogenous human proteins.

A wide variety of ligand binding domains may be used in this invention, although ligand binding domains which bind to a cell permeant ligand are generally preferred. It is also preferred that the ligand have a molecular weight under about 5kD, more preferably below 2.5 kD and optimally below about 1500 D. Non-proteinaceous ligands are also preferred. Ligand binding domains include, for example, domains selected or derived from (a) an immunophilin (e.g. FKBP 12), cyclophilin or FRAP domain; (b) a hormone receptor such as a receptor for progesterone, ecdysone or another steroid; and (c) an antibiotic receptor such as a tetR domain for binding to tetracycline, doxycycline or other analogs or mimics thereof.

A tetR domain useful in the practice of this invention may comprise a naturally occurring peptide sequence of a tetR of any of the various classes (e.g. class A, B, C, D or E) (in which case the absence of the ligand stimulates target gene transcription), or more preferably, comprises a mutated tetR which comprises at least one amino acid substitution, addition or deletion compared to a wild-type tetR, especially those mutated tetR domains in which the presence of the ligand stimulates target gene transcription in a cell engineered in accordance with this invention. For example, mutated tetR domains include mutated Tn10-derived tetR domains having an amino acid substitution at one or more of amino acid positions 71, 95, 101 and 102. By way of further illustration, one mutated tetR comprises amino acids 1 - 207 of the Tn10 tetR in which glutamic acid 71 is changed to lysine, aspartic acid 95 is changed to asparagine, leucine 101 is changed to serine and glycine 102 is changed to aspartic acid. Ligands include tetracycline and a wide variety of analogs and mimics of tetracycline, including for example, anhydrotetracycline and doxycycline. Target gene constructs in these embodiments contain a target gene operably linked to a transcription control sequence including one or more copies of a DNA sequence recognized by the tetR of interest, including for example, an upstream activator sequence for the appropriate tet operator. See e.g. US Patent No. 5,654,168, the full contents of which are expressly incorporated by reference.

Conclusion

Again, applicants appreciate the Examiner's time and thought on this important case. The case is now considered to be in condition for allowance, which is respectfully requested at this time. If it might be helpful in answering any questions or otherwise advancing prosecution, applicants again invite the Examiner to call their attorney at the number provided below.

Respectfully submitted,

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